

among the group of non-pathogenic microorganisms that constitutes an overwhelming majority in the ecological system of nature, and it is also amplifying propagation of the multiple drug resistance among pathogenic bacteria, directly or indirectly: such possibility is apprehended. (M. Yoshikawa, Bull. of Jap. Soc. of Microbial Ecology, 10, No. 3, 141-148 (1995).)

Please rewrite the paragraph from page 3, line 26 to page 4, line 18 as follows:

In the traditional concept in pharmaceutical sciences, it has been fundamentally believed that drugs can not exert their intrinsic effects if they have been converted to the immobilized state, and that they can do so only in cases where they are used in their free state. Accordingly, no provisions exist in the laws and rules of the world pertaining to the manufacture, the use, the approval, and the like of drugs that deal with drug-immobilized polymer substrate preparations in which low-molecular weight drugs are allowed to be linked to polymer substances so as not to cause liberation of the drugs and which can exert therapeutic effects without involving the liberation. To put it differently, in the case of medicinal preparations where low-molecular weight drugs are immobilized to polymer substances, it has been believed that the liberation of the drugs is an essential prerequisite when they are allowed to act on targets like the controlled-releasing preparations stated above. It can be said that there has been no need to make the controlling laws and regulations, because the drugs have been believed to be totally ineffective if their liberation does not occur.

Please rewrite the paragraph on page 14, lines 11-26 as follows:

Here, the expression "exerts (the) selective biological activity" means that substantially no harm or tolerable adverse reactions are brought to a host environment (nature, a host animal or plant, cells, and organelle, and the like) and that the biological activity is exerted against a harmful, target agent the elimination or the control of which is wanted. Therefore, chemotherapeutics are mentioned as the biologically active compounds exerting their selective biological activity. The chemotherapeutics are drugs having high selective toxicity that causes only damage to harmful agents to be targeted without damaging hosts. The objects of chemotherapeutics are not limited to living things such as pathogenic microorganisms or harmful animals and plants, but extend to a considerably

133
cont

wide range, including cells such as malignant tumors, and non-living matters such as enzymes, receptors, and hormones.

2 Please rewrite the paragraph on page 18, lines 8-16 as follows:

Among preferable drugs which can be utilized in this invention, those described below can be illustrated as the most important chemotherapeutics:

D4

griseofluvin, vernamycin B, ostreogrycin G, isoniazid, benzonaphtacequinones such as benanomycin and pradimicin, pyridoxine, PAS, pimaricin, fungichromin, formycin, toyocamycin, chloramphenicol, tetracycline, streptomycin, erythromycin, ampicillin, norcardicin, SQ 83360, and OA-6129, and the like.

3 Please rewrite the paragraph on page 21, lines 2-10 as follows:

D5

Mentioned as other organic polymers are natural organic polymers and modified natural organic polymers, which have been conventionally used to form the substrates for gel filtration, ion-exchange chromatography, affinity chromatography or the like. To specifically name these: cellulose, agarose, glucomannan, chitosan, pullulan, starch, dextran, and the like. Conventionally, the substrates for use in affinity chromatography and the like have been processed as porous spheres of these natural organic polymers.

4 Please rewrite the paragraph from page 25, line 24 to page 26, line 7 as follows:

D6

The functional groups that can be used at "the active site provided on the substrate," or at "the active site provided at the graft chain branched from the substrate," or at "both termini of the spacer (may not be the same groups)," or at "the specified position of the biologically active compound for linking" and that can be mentioned are, for example, as follows:

a double bond, a triple bond, an amino group, an epoxy group, a glyceryl group, an isocyanate group, an aldehyde group, a carboxyl group or a derivative thereof (e.g., an ester group, an anhydrous carboxylic acid group and a halogenated carbonyl group), an allyl group, and the like.

17 Please rewrite the paragraph from page 28, line 22 to page 29, line 2 as follows:

When R^1 is a cation, it represents a carboxylate. The cation is not particularly limited, and may be either an inorganic cation or an organic cation. Mentioned as the inorganic cation are an alkaline metal cation such as sodium ion or potassium ion, an alkaline earth metal ion such as calcium ion, a transition metal ion such as ferric ion (or ferrous ion), a complex ion, and the like. Mentioned as the organic ion is, for example, an ammonium ion such as a tetraalkylammonium ion.

18 Please rewrite the paragraph from page 32, line 27 to page 33, line 9 as follows:

Further, in this invention the immobilization of a biologically active compound has a purpose of preventing the biologically active compound from freely moving and diffusing within its environment. Therefore, when the biologically active compound is immobilized to the spherical substrate described above, it is preferred that the immobilization be conducted so that the spherical substrate may not disperse into the treatment space (e.g., a filtration bed provided on the passageway for filtering the air containing treatment objects) of objects to be treated (bacteria, molds, and the like).

19 Please rewrite the paragraph from page 40, line 27 to page 41, line 5 as follows:

Another example of utilization of the biologically active polymer products of this invention is use forms that suppose the use for considerably long hours. For example, the polymer products of the invention that have been processed into sheet forms, paint forms, or fibrous forms may be utilized as clothes, curtains, sheets, paint products, external films, sanitary goods, and the like.

20 Please rewrite the paragraph from page 41, line 24 to page 42, line 12 as follows:

A nonwoven fabric having a METSUKU (weight per unit area) of 50 g/m^2 and a thickness of 0.4 mm, which was made of polypropylene (available from Mitsui Petrochemical Ind. Co.; the trade name: Syntex PS-110), was irradiated 200 kGy with electron beam (at 2 MeV and 1 mA) under a nitrogen atmosphere. Then, these fibers were immersed in a monomer solution of acrylic acid/methanol (1/9) and were allowed to react at 40°C for 4 h. Consequently, fibers having an acrylic

acid graft rate of 78.5% were produced, which are hereinafter referred to as the "grafted fibers with carboxyl groups." The ion-exchange capacity of the grafted fibers with carboxyl groups was 6 meq/g.

Here, the graft rate was calculated according to the following formula:

graft rate = $\{(\text{weight of substrate after graft formation} - \text{weight of substrate before graft formation}) / \text{weight of substrate before graft formation}\} \times 100(\%)$

Please rewrite the paragraph from page 44, line 10 to page 45, line 5 as follows:

FIG. 2 shows the results from a test of antimicrobial activity of these ampicillin-immobilized sample and control sample against Staphylococcus aureus FDA 209P, as assayed by the rapid evaluation method for antibiotic activities. As is apparent from FIG. 2, the sample having immobilized ampicillin in the presence of carbodiimide displays distinct antimicrobial activity, whereas the sample having undergone similar treatment in the absence of carbodiimide displays no antimicrobial activity at all. This demonstrates that non-specific adsorption of ampicillin to the substrate has not occurred under the immobilization and aftertreatment conditions used here. Further, under similar testing and evaluation conditions, this ampicillin-immobilized grafted fibers with carboxyl groups displayed antimicrobial activity against Bacillus subtilis ATCC6623, Bacillus anthracis, Staphylococcus aureus K2, Staphylococcus aureus Smith, and Myrococcus luteus ATCC9341, and the like. However, even this ampicillin-immobilized sample was ineffective against Escherichia coli NIHJ, Proteus vulgaris OX-19, Klebsiella pneumoniae PCI602, Candida albicans 3143, Aspergillus niger, etc. Namely, it can be said that the ampicillin-immobilized grafted fibers with carboxyl groups according to this invention exert the selective biological activity that is peculiar to ampicillin.

IN THE CLAIMS

Cancel, without prejudice to the subject matter involved, claims 16 and 29.

Please amend claim 1 as follows:

1. (Thrice Amended) A biologically active polymer product having:
a water-insoluble graft polymer substrate; and